REMARKS

Claims 51-94 were pending in the application. Claims 61-70, 79-83, and 91-94 are cancelled without prejudice as being directed to a non-elected invention. Claims 51-56, 71, 74-76, 78, 84-87, and 89 have been amended. New claims 95-117 have been added. Accordingly, claims 51-56, 58-60, 71-78, 84-90, and 95-117 are pending following entry of this amendment. The specification has been amended to include reference to SEQ ID NO: 1. Attached hereto is a "Version With Markings to Show Changes Made" which is a marked-up version of the changes made to the claims by the current amendments.

Support for the amendments to claims 51-56, 71, 74-76, 78, 84-87, and 89 can be found in the claims as originally filed and throughout the specification. Additional support for the amendments to claims 53, 75, and 86, can be found in the specification at least at page 29, lines 12-19. Support for new claims 95-117 can be found in the claims as filed and throughout the specification, including at page 46, lines 10-16 and at page 48, lines 16-20. No new matter has been added.

Amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of Claims 53, 58-60, 71-78, and 84-90 Under 35 U.S.C. § 112, Second Paragraph

I. Rejection of Claims 53, 75, and 86 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 53, 75 and 86 under 35 U.S.C. § 112, second paragraph for recitation of the word "functional" as being unclear "as to the extend [sic] of functionality required from the amino acid sequence." Applicants respectfully traverse this rejection. As amended, claims 53, 75, and 86 are directed to methods which include the use of soluble lymphotoxin-β receptor (LTβ-R), wherein the ligand binding domain comprises SEQ ID NO: 1, or a functional fragment thereof. SEQ ID NO: 1 corresponds to the extracellular portion of the human LTβ-R

(see page 29, lines 8-10 of the specification). The specification teaches that functional fragments are amino acids which contain ligand binding domains, including those which can compete with LTβ receptors for LT ligand binding as well as fragments useful in inhibiting the humoral response as claimed. Thus, the term "functional" is clearly defined and supported by the teachings of the instant specification. Applicants respectfully request that in view of the teachings of the specification, the rejection of claims 53, 75 and 86 under 35 U.S.C. § 112, second paragraph be withdrawn.

II. Rejection of Claim 71 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claim 71 under 35 U.S.C. § 112, second paragraph for recitation of the phrase "effective amount." Applicants have amended claim 71 to a method for inhibiting LT-β receptor signaling without inhibiting TNF-R signaling in a subject comprising administering to a subject a pharmaceutical composition comprising an amount of a soluble lymphotoxin-β receptor (LTβ-R). In view of the amendment to claim 71, Applicants respectfully request that the rejection under 35 U.S.C. § 112 be withdrawn.

III. Rejection of Claims 84-90 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claim 84 and dependent claims thereof under 35 U.S.C. § 112, second paragraph for using the term "association" which the Examiner asserts is unclear. Applicants respectfully traverse this rejection. Claim 84 is directed to a method for disrupting the association of immune complexes and B cell follicles in a patient comprising administering an amount of a soluble lymphotoxin-β receptor (LTβ-R) to said patient. Applicants assert that the term "association" is a term of art that would be recognized by one of ordinary skill. Furthermore, the specification clearly supports use of the term "association." For example, at page 22, lines 14-34 of the specification, Applicants describe that the claimed invention can be used to disrupt or prevent the trapping of immune complexes by B cell follicles. Applicants also describe immune complexes as being bound to follicular dendritic cells, where they are recognized by B cells. Accordingly, Applicants respectfully request that the rejection of claims 84 and those that depend therefrom under 35 U.S.C. § 112, second paragraph be reconsidered and withdrawn.

Rejection of Claims 51-60, 71-78 and 84-90 under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 51-60, 71-78 and 84-90 under 35 U.S.C. § 112, first paragraph. The Examiner states that "because the specification, while being enabling for a method of inhibiting a humoral response comprising the administration of a LT-β-R-Ig fusion, does not reasonably provide enablement for a method of inhibiting a humoral response or a method of inhibiting LT-β-R signaling comprising the administration of a soluble LT-β-R." Applicants respectfully traverse this rejection.

The claimed invention is directed to a method for inhibiting a humoral immune response in an animal comprising administering to the animal a pharmaceutical composition which comprises a therapeutically effective amount of a soluble lymphotoxin–β receptor (LTβ-R). The invention also describes a method for inhibiting LTβ-R signaling without inhibiting TNF-R signaling in a subject comprising administering to a subject a pharmaceutical composition comprising an amount of a soluble LTβ-R. The invention is further directed to a method for disrupting the association of immune complexes and B cell follicles in a subject comprising administering to the subject a pharmaceutical composition comprising an amount of a soluble LTβ-R to said patient.

In the specification, Applicants provide numerous examples of LT-beta blocking agents and LT-beta-R blocking agents, including soluble LTβ-R and soluble LTβ-R-Ig fusions. Applicants teach how to obtain soluble LTβ-R molecules, for example, by cloning SEQ ID NO: 1 (which corresponds to the extracellular portion of LTβ-R), or a functional fragment thereof, into an expression vector and expressing the soluble LTβ-R molecule in the appropriate host cell (page 29, lines 7-19 of the specification). Applicants also teach that a soluble LTβ-R molecule can be fused with a heterologous protein domain, such as stable plasma proteins, in order to increase the stability of the LTβ-R fusion protein or to modulate its activity (page 29, lines 20-34 of the specification). Thus, the specification describes many examples of soluble LTβ-R molecules, which include but are not limited to a LTβ-R-Ig fusion protein.

The Examiner asserts that "the specification is devoid of any explanation of detailed example showing how the administration of soluble LTβ-R is capable of inhibiting the signaling of LTβ-R." The Examiner also asserts that "[t]he working examples of the instant application discloses the capability of LTβ-R-Ig proteins to disrupt humoral responses, however, no where in

the specification does it teach...how to disrupt or inhibit a humoral response through the administration of a soluble LTβ-R." As described by the Examiner, Applicants provide working examples using a soluble LTβ-R fusion protein, namely a LTβ-R-Ig fusion, which demonstrate that soluble LTβ-R molecules can inhibit the humoral response in a subject. In support of this position, Applicants provide working examples ***which demonstrate that blocking the lymphotoxin pathway alters the humoral response in an animal***. This was unexpected at the time of Applicants' invention in view of the fact that this pathway was previously shown to be involved with T-cell mediated immune responses. Applicants discovered that administration of LTβ-R blocking agents interferes with the presentation of antigens on follicular dendritic cells (FDCs), which is likely to be important in antibody-mediated autoimmune diseases (see page 21, lines 8-15 and page 22, lines 3-31 of the specification). In fact, in one the working example, Example 4, Applicants demonstrate that mice injected with a LTβ-R-Ig fusion for 6 weeks lack FDCs (see, e.g., page 39 of specification). In addition, Example 7 shows that LTβ-R-Ig-treated mice primed with SRBC show an altered humoral immune response due to the failure of germinal centers (GC) to form in the spleen. As described at page 45, line 1 to page 46, line 7, mice treated with LTβ-R-Ig showed "complete inhibition of IgG responses and an abbreviated/diminished IgM responses relative to the controls." Thus, Applicants respectfully submit that in contrast to the Examiner's assertion, Applicants teach "how to disrupt or inhibit a humoral response through the administration of a soluble LTβ-R."

One of ordinary skill in the art would recognize that the working examples provided in the instant specification demonstrate that inhibition of the LT pathway is necessary for the achieved results, and not that the results are specific to the use of a particular LTβ-R-Ig fusion. Applicants submit that the data presented in the specification supports the claimed invention and therapeutic uses thereof, and should not be used to limit the scope of the claimed invention. ***The LTβ-R-Ig fusion protein described in the working example is representative of the claimed soluble LTβ-R molecule described in the specification.*** Applicants provide ample working examples using LTβ-R-Ig, such that one of ordinary skill in the art would have a reasonable expectation of success based on the teachings of the instant examples. Furthermore, Applicants describe how to make soluble LTβ-R molecules other than the LTβ-R-Ig fusion used in the

working examples, so that one of ordinary skill in the art would not require undue experimentation to achieve the claimed invention.

In order to meet the enablement requirement, it is not necessary that a patent specification include specific examples of every different embodiment encompassed by the claims. Moreover, the fact that some experimentation may be necessary, does not constitute lack of enablement as long as the amount of experimentation is not unduly extensive. *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1213 (CAFC 1991). A considerable amount of experimentation is permissible if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands* 8 USPQ2d 1400-1407, 1404 (CAFC, 1988).]

In view of the teachings in the specification and the general knowledge in the art, the specification has provided sufficient guidance to the ordinarily skilled artisan as to how to make and use the invention. Accordingly, the specification meets the enablement requirement and Applicants respectfully request that the rejection of claims 51-60, 71-78 and 84-90 under U.S.C. 112 first paragraph be withdrawn.

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

Please amend the paragraph which is found at page 11, lines11-12 as follows:

(Amended) ---**Figure 1** is a sequence (SEQ ID NO: 1) of the extracellular portion of the human LTβ receptor which encodes the ligand binding domain.---

In the claims:

51. **(Amended)** A method for inhibiting a humoral immune response in an animal comprising administering a pharmaceutical composition comprising ~~which comprises~~ a therapeutically effective amount of a soluble lymphotoxin-β receptor (LTβ-R).

52. **(Amended)** The method according to claim 51, wherein the soluble LTβ-R ~~lymphotoxin-β receptor~~ comprises a ligand binding domain that can selectively bind to a surface LT ligand.

53. **(Amended)** The method according to claim 51, wherein the ligand binding domain comprises ~~a functional sequence of amino acids selected from the amino acids of~~ SEQ ID NO: 1 ~~(Figure 1)~~, or a functional fragment thereof.

54. **(Amended)** The method according to claim 51, wherein the soluble LTβ-R ~~lymphotoxin-β receptor~~ further comprises one or more heterologous protein domains.

56. **(Amended)** The method according to claim 51, wherein the soluble LTβ-R ~~lymphotoxin-β receptor~~ comprises a human immunoglobulin Fc domain.

71. **(Amended)** A method for inhibiting LT-β receptor signaling without inhibiting TNF-R signaling comprising the step of administering to a subject a pharmaceutical composition comprising an ~~effective~~ amount of a soluble lymphotoxin-β receptor (LTβ-R).

74. **(Amended)** The method according to claim 71, wherein the soluble ~~lymphotoxin-β receptor~~ LTβ-R comprises a ligand binding domain that can selectively bind to a surface LT ligand.

75. **(Amended)** The method according to claim 71, wherein the ligand binding domain comprises ~~a functional sequence of amino acids selected from the amino acids of~~ SEQ ID NO: 1 ~~(Figure 1),~~ or a functional fragment thereof.

76. **(Amended)** The method according to claim 71, wherein the soluble LTβ-R ~~lymphotoxin-β receptor~~ further comprises one or more heterologous protein domains.

78. **(Amended)** The method according to claim 71, wherein the soluble LTβ-R ~~lymphotoxin-β receptor~~ further comprises a human immunoglobulin Fc domain.

84. **(Amended)** A method for disrupting the association of immune complexes and B cell follicles in a patient comprising administering an amount of a soluble lymphotoxin-β receptor (LTβ-R) to said patient.

85. **(Amended)** The method according to claim 84, wherein the soluble LTβ-R ~~lymphotoxin-β receptor~~ comprises a ligand binding domain that can selectively bind to a surface LT ligand.

86. **(Amended)** The method according to claim 85, wherein the ligand binding domain comprises ~~a functional sequence of amino acids selected from the amino acids of~~ SEQ ID NO: 1 ~~(Figure 1)~~ or a functional fragment thereof.

87. **(Amended)** The method according to claim 84, wherein the soluble LTβ-R ~~lymphotoxin-β receptor~~ further comprises one or more heterologous protein domains.

89. **(Amended)** The method according to claim 84, wherein soluble LTβ-R ~~lymphotoxin-β receptor~~ further comprises a human immunoglobulin Fc domain.